Normal and Delayed Pubertal Development

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You don't have to suffer to be a poet; adolescence is enough suffering for anyone.

― John Ciardi

Learning Objectives:
1. Understand and identify normal pubertal development in males and females
2. Become familiar with the common causes of delayed puberty in males and females
3. Develop an evaluation and management plan for a child with delayed puberty

Primary Reference:
   http://pedsinreview.aappublications.org/content/pedsinreview/37/7/292.full.pdf

CASE ONE:

Tim Tiny is a 15-year-old male who presents for a well child visit. He is concerned that he is shorter than most of his classmates and has not started shaving like some of his friends. To make matters worse, Tim’s 12-year-old sister, Bertie Pew has grown 2 inches over the past year and is now taller than he is!

1. What are the events in normal pubertal development? What is the timing in a female? In a male?

Puberty is the process of normal sexual maturation culminating in full reproductive capability. Pubertal changes are due to increased secretion of sex steroids (gonadarche). In both females and males, these increases are secondary to increased secretion of the pituitary gonadotropins: luteinizing hormone (LH) and follicle stimulating hormone (FSH). In males, LH causes increased production of testosterone, while FSH stimulates maturation of spermatogonia. In females, both LH and FSH are responsible for sex hormone production, while FSH plays a larger role in ova maturation.

Prior to puberty, secretion of gonadotropin-releasing hormone (GnRH) is minimal, limiting the release of LH and FSH. Puberty begins with the initiation of a specific pattern of pulsatile release of GnRH through a currently unknown mechanism. At the onset of puberty, the amplitude of LH release increases dramatically, at first during sleep but then progressing throughout the day as the body matures. This synchronized episodic increase in LH/FSH stimulation sets into motion ovulation and spermatogenesis.

Adrenarche, the rise in the secretion of adrenal androgens, (DHEA, androstenedione) precedes gonadarche by several years in both males and females. It is these adrenal androgens that are responsible for the early growth of pubic and axillary hair, apocrine gland development as well as some degree of acne and body odor. These first signs of adrenarche typically appear 6 months after the earliest signs of gonadarche. It is unknown what triggers the activation of the hypothalamic-pituitary-adrenal axis and it has been demonstrated that the timing of adrenarche does not significantly affect the onset of gonadarche.

Over the past few years, investigators have begun to tackle the genetic and epigenetic programming of puberty. Work stemming from patients with Kallman syndrome and hypogonadotropic hypogonadism have identified pathways including kisspeptin/GPR54 and KAL1 respectively, which need to function appropriately for the initiation and progression of puberty. This work is in its infancy, however, and the overall genetic control of puberty is far from clear.
Moderators can refer learners to figures 4 and 5 in Rosen’s article “Physiologic growth and development during adolescence” as a visual aid to assist with the following discussion.

The average onset of puberty in females is 11 years, but may normally begin over a wide range of years, most often cited as 8-14 years of age. The average duration of pubertal development is 3 years, but it may conclude in as few as 2 and as many as 6 years. A rise in estradiol heralds the onset of gonadarche with the development of breast, genital, and uterine maturation and a redistribution of fat into more womanly contours.

Thelarche, the onset of breast development, is usually the first visible evidence of puberty in girls. This is typically followed by the growth of pubic hair within the next 6 months. The onset of the pubertal growth spurt coincides closely with these two events and peak height velocity is attained by Tanner Stages II-III. Menarche usually occurs 2 years after the onset of pubertal breast growth and coincides with Tanner Stage IV. After menarche, the average girl will grow an additional 4 to 6 cm (with considerable variation), but will usually complete linear growth within two years. Generally, early menarche is correlated with shorter adult height.

The average onset of puberty in males is later than in females, typically at the age of 12 with a normal range from 8-14 years of age. During puberty, there is an up-regulation of the hypothalamic-pituitary-testicular axis resulting in increased circulating levels of LH, FSH, and testosterone, which drive testicular maturation as well as the virilization of physical features including increased muscle mass and voice deepening.

Increasing testicular size and volume is the first visible evidence of gonadarche, though many patients will not recognize that they have entered puberty until the growth of pubic hair which typically occurs within 6 months of testicular changes. The pubertal growth spurt also happens later in males, who attain peak height velocity during mid-puberty at Tanner Stage IV. This coincides with the onset of virilization, as well as the presence of gynecomastia in up to 50% of all males. Facial hair growth occurs about 3 years after the onset of pubic hair growth. The duration of puberty is longer in males, lasting on average 5 years, allowing for greater linear growth than in females.

2. Do Tim’s symptoms meet the definition for delayed puberty? If so, what questions would be important to ask during your history? What are the key elements of the physical exam and further diagnostic evaluation?

Delayed puberty is defined by the lack of pubertal changes in girls by 13 years or in boys by 14 years of age. Additionally, any patient who appears to have experienced an arrest in pubertal development after entering into puberty should be evaluated thoroughly. Begin with a complete history, including previous CNS surgery, chemotherapy, or radiation, as well as a detailed family history.

Physical exam should make careful note of weight, height, and Tanner stage. Upper and lower segment ratios can be calculated (a decreased ratio is seen in Klinefelter syndrome). A thorough genital exam, including assessment of testicular size, location, and consistency must be preformed. Prepubertal testes are usually 1 cm or less along the longitudinal axis and have a rubbery consistency, while a testis longer than 2.5 cm has undergone some pubertal growth. Nonpalpable or particularly firm or soft testes suggest a pathologic condition. Additionally, a careful neurological exam should be completed including fundoscopic exam, visual fields, and cranial nerve testing (including sense of smell to rule out Kallmann Syndrome).

The initial diagnostic approach for both sexes includes reviewing weight gain and linear growth, obtaining a bone age, and exploring any other evidence of endocrinopathy such as panhypopituitarism or hypothyroidism. Laboratory investigations should include early morning serum LH and FSH levels, thyroid function studies, morning total testosterone level (in males), and estradiol (in females). All patients who have not shown any evidence of pubertal development by age 13 (girls) or 14 (boys) should be referred to an endocrinologist for further evaluation.

3. What are the diagnostic and treatment possibilities for delayed puberty?
The list of conditions leading to delayed puberty is extensive; however, the differential diagnosis can be simplified when divided into two categories based upon serum gonadotropin levels: 1) normal/low (constitutional delay and hypogonadotropic hypogonadism) and 2) elevated (hypergonadotropic hypogonadism). Learners can refer to table 2 in Wolf and Long’s article “Pubertal Development” to guide the discussion.

**Conditions presenting with normal or low serum gonadotropins:**

The classic common form of delayed puberty is properly called constitutional delay of adolescent development, and reflects a benign but delayed program of maturation. These patients are healthy but have a history of delayed growth throughout childhood (i.e., short stature with a normal growth rate). Family History is likely to reveal the presence of delayed pubertal onset in one or both parents or in siblings. Physical exam will not reveal any abnormalities except pubertal delay. Assessment of growth velocity will be appropriate for the Tanner Stage noted on physical examination, and height age will typically correspond with the bone age, which is often delayed by 2 or more years. Laboratory evaluation is normal, with the possible exception of low (prepubertal) serum gonadotropin levels.

Although most males who present with normal but underdeveloped genitalia and delayed pubertal development have constitutional delay, it is important to rule out other etiologies of hypogonadotropic hypogonadism.

**Hypogonadotropic hypogonadism** results from any condition which impairs or prevents either the hypothalamus from secreting GnRH or the pituitary from secreting FSH and LH. Many of these conditions can be readily identified on history, physical exam, or laboratory evaluation as detailed above. This category includes CNS processes that disrupt the hypothalamic-pituitary axis including tumors and granulomatous diseases; endocrinopathies such as hypothyroidism, prolactinoma, and panhypopituitarism; chronic disease; malnutrition; and eating disorders. A variety of genetic syndromes such as Prader-Willi, Lawrence-Moon, and Bardet-Biedel may also be considered. A finding of anosmia suggests Kallman syndrome, the most common form of isolated gonadotropin deficiency.

Unfortunately, once the above conditions have been ruled out, it is difficult to differentiate severe constitutional delay from an isolated gonadotropin deficiency. Nearly all patients with constitutional delay will spontaneously enter puberty by 18 years of age, therefore an approach of watchful waiting can be considered. This approach may not be acceptable to all patients, however, given the psychosocial stress associated with pubertal delay. In these cases, an alternative is to administer hormonal stimulation with a short course of low dose testosterone. Therapy results in appreciable sexual development and may trigger puberty. Most patients will continue to progress through puberty and require no further treatment, though they should be monitored through the end of puberty. Those patients who do not progress, and who demonstrate persistently low LH, FSH, and testosterone, are likely to have true hypogonadotropic hypogonadism and require testosterone therapy to achieve and maintain secondary sex characteristics.

**Conditions presenting with elevated serum gonadotropins:**

**Hypergonadotropic hypogonadism,** (also known as primary hypogonadism or testicular failure) results from any condition which disrupts the production of sex steroids leading to elevated serum gonadotropins via a lack of negative feedback on the hypothalamic-pituitary axis. The most common cause of testicular failure is Klinefelter syndrome, which should be suspected in any tall thin adolescent without evidence of pubertal development. Other etiologies of testicular failure which could be elicited include iatrogenic causes such as chemotherapy or radiation, trauma, infections (mumps), or autoimmunity. Many of these patients will not have obvious physical or historical findings and will only be identified by laboratory evaluation of gonadotropin levels.

With hormone replacement, which should begin at the usual age of pubertal onset, these boys will be able to develop male secondary sex characteristics and have normal sexual function. However, these patients are not likely to be able to conceive their own children. Prosthetic testes are often used in these patients for cosmetic reasons.

4. How would your approach change if the situation was reversed and it was his sister presenting at 15 with delayed puberty?
Although fewer females than males present with delayed puberty, those that do are more likely to have a pathological cause of their delay. Just as for males, the differential diagnosis of delayed puberty for females can be divided into two categories: normal or low serum gonadotropins, and increased serum gonadotropins. Gonadotropin levels and bone age should be obtained in addition to a careful history to clarify family history, chronic illness, or endocrinopathy. As in boys, physical examination is critical to the evaluation and should focus on body proportions, weight, height velocity, breast and genital development, neurologic exam, and evidence of Turner syndrome including webbed neck, shield chest and widely spaced nipples.

**Hypogonadotropic hypogonadism** in females can result from many of the same conditions as previously discussed for males. The differential includes endocrinopathies such as panhypopituitarism, prolactinoma, and hypothyroidism, as well as other conditions such as prolonged illness, chronic glucocorticoid therapy, excessive stress (either physical or emotional), or starvation. Kallman syndrome is less likely in females as the most common defect is X-linked. In patients with low gonadotropins, normal secretion may occur if the underlying problem is corrected. Once these etiologies have been ruled out, it is again difficult to sort out constitutional delay from an isolated gonadotropin deficiency. Constitutional delay is far less common in females, though it does occur. These patients should be evaluated for hormone replacement therapy consisting of cyclic estrogen-progesterone therapy.

Females found to have **hypergonadotropic hypogonadism** should have a karyotype sent to evaluate for Turner Syndrome, the most common cause of gonadal failure. Once this has been ruled out, other etiologies such as primary ovarian failure and autoimmune endocrinopathies should be entertained, as well as other acquired causes as discussed above. Treatment for these patients once again consists of hormone replacement which will produce the development of secondary sex characteristics but generally will not result in fertility.

**Additional References:**

**Resources:**